REMARKS

I. Status of the Claims

Claims 1-36 and 38-66 are pending, with claims 8, 11, 13-18, 20-35, and 38-68 withdrawn as directed to a non-elected invention. Thus, claims 1-7, 9-10, 12, 19 and 36 were under examination. Upon entry of this amendment, claims 1-7, 10 and 21 are amended and claims 8-9, 11-20, 22-67 canceled without prejudice or disclaimer. These amendments are made to focus the claims on subject matter of current commercial importance. Applicants retain the right to prosecute the original claims in this or another application. New claims 68-79 are also introduced upon entry of this amendment.

The amended and new claims find support throughout the specification including, for example, the following sections:

Claims 1, 68: page 28, line 29; page 32, line 34; Table A; page 33, line 1; page 32, lines 27-28; page 97, line 30; page 54, line 29 to page 57, line 23; and Example 10

Claims 69: page 58, lines 20-21.

Claim 70: page 56, lines 9-12

Claim 71: page 56, lines 15-17

Claim 72: page 56, lines 20-22

Claim 73: page 57, lines 1-2

Claim 74: page 57, lines 3-4

Claim 75: page 57, lines 4-7

Claim 76: page 102, lines 12-13; and Table D

Claim 77: page 102, lines 13-14; and Table D

Claim 78: example 10

Claim 79: page 7, lines 25-27

II. Restriction and Species Election Requirement

The currently pending claims all fall within the Group II set of claims as set forth in the Restriction Requirement in the parent application. Reconsideration of the species election

requirement is requested. If a species election is required, Applicants request an opportunity to select a different species than requested in the parent application as permitted under MPEP 819 for Continued Prosecution Applications.

III. Amendments to the Specification

A specific reference to the priority application for this case has been added as requested by the Examiner.

IV. Claim Objections

The claims are objected to as reading on non-elected subject matter. The claims have been amended to specifically recite to protein markers so the claims fall within the elected subject matter. Claim 21 in particular has been amended to clarify that it refers to certain protein markers. Because the claim now clearly falls within the elected group, it is requested that this claim be rejoined and examined together with the other elected claims.

Claims 1 and 36 were objected to for use of the word "perform" rather than "performing." Claim 1 has been amended to remove the performing step and claim 36 has been canceled, thus rendering this rejection moot.

V. Claim Rejections under 35 U.S.C. 112, first paragraph

Claims 1-7, 9, 10, 12, 19 and 36 stand rejected as allegedly lacking sufficient description to enable one to practice the invention as defined in the claims. For the reasons that follow, Applicants respectfully disagree.

As the Office Action correctly notes, the test for determining whether a claim is enabled is to determine whether the claimed invention can be practiced by one of ordinary skill in the art without undue experimentation. With respect to the currently pending claims, the issue thus is whether the skilled artisan can without undue experimentation: 1) determine the level of one or more protein markers for macular degeneration, and 2) assess whether these levels differ

from the levels for the same marker(s) in a control population. The answer to both questions is yes.

With respect to issue 1, the application describes various immunological, immunohistochemical, Western blot and ELISA techniques for detecting various protein markers associated with macular degeneration (see, e.g., page 55, line 7 to page 59, line 16; and example 10). Immunological techniques and Western blot analysis for proteins were also well known in the art as of the priority date of this application. One of ordinary skill then could determine the presence of protein markers associated with macular degeneration without undue experimentation.

Turning to issue 2, one of ordinary skill could also establish whether the level of the one or more protein markers in the subject differed from those in a control population without undue experimentation. The application, for instance, includes guidance on certain protein markers that are increased or decreased relative to a control (see, e.g., examples 9 and 11). Moreover, since the application identifies the appropriate protein markers to detect, those of ordinary skill could readily assess the relative levels of the marker(s) for the subject and an appropriate control of their choosing using the protein analyses described in the application or those generally known in the art. It is thus submitted that this aspect of the claims is also fully enabled.

The Office Action, however, makes three primary arguments with respect to issue 2 to conclude that the claims are not enabled: 1) the application and claims do not present a standard that one could utilize to diagnosis whether a subject has an aortic aneurysm or a predisposition to such a disease, 2) the application fails to establish a correlation between markers of macular degeneration and aortic aneurysm, and 3) guidance in the application with respect to detecting certain markers as an indicator of an aortic aneurysm is contrary to teachings in the scientific literature. These specific issues will be addressed in turn.

With respect to argument 1, Applicants note that the claims have been amended to recite an explicit standard so one of ordinary skill can ascertain whether the level determined for a maker (or markers) is correlated with risk for an aortic aneurysm at a location other than the

eye. More specifically, claim 1 has been amended to state that "a difference in the level of the one or more protein markers relative to the level of the same marker(s) in a control population is an indication that the subject is at risk for an aortic aneurysm at a location other than an artery in the eye." The claim further clarifies that the control population is one or more individuals, at least one of which does not have the aneurysm and/or macular degeneration. So one of ordinary skill can determine what change in marker level is relevant in view of this explicit standard. Furthermore, as noted above, determination of protein levels can be determined without undue experimentation using the methods described in the application and known in the art.

The second contention generally is that the application fails to provide convincing evidence that there is a correlation between macular degeneration and aortic aneurysm. The Office Action particularly notes that the statistical results described in example 1 appear contrary to the conclusion made in the claims. With regard to this general argument, Applicants reiterate the point made in the prior response, namely that the application provides ample evidence to establish that there is a reasonable correlation between the two diseases. Applicants again direct the Examiner's attention to pages 67-68 that provide an extensive list of results that establish a correlation between the two diseases. Examples of such findings include, but are not limited to:

1. One study analyzing over 207 eyes (including eyes from individuals with and without AMD and/or AAA) found a strong statistical correlation between AAA and neovascular AMD ($P<0.00001$).

2. In a clinical trial, 5 of 8 individuals having classical AAA fundus phenotype also had AMD.

3. Histochemical and biochemical results indicate that arterial disease plaques and drusen (a significant risk factor for macular degeneration) have similar composition, suggesting similar pathways in the etiology of the arterial disease and macular degeneration.

4. Ultrasound and immunohistochemical results from 151 individuals showing that the type of collagen deposits observed in certain arterial diseases are also observed in macular degeneration.

5. The presence of autoantibodies that specifically bind proteins associated with retinal pigment epithelium, retina and drusen in the serum of individuals with AAA and/or AMD.

6. Results from gene array analyses showing similarity in genes that are up- or down-regulated in individuals having AAA and/or AMD.

Individually and collectively these findings demonstrate that macular degeneration and aortic aneurysms are correlated and indicate that these diseases share similar mechanisms.

Turning to the assertion that the results presented in Example 1 are contrary to what is claimed, Applicants make two points. First, it is noted that the claims have been amended to clarify that the method is one for assessing whether a subject is at risk for aortic aneurysm. So the claim does not require that every subject determined to have a protein marker for macular degeneration have an aortic aneurysm. Secondly, the Office Action fails to consider the results with respect to the correct population. One value of the current methods is to identify those individuals from the *general population* (e.g., a population including individuals with and without aortic aneurysm and/or macular degeneration) that are at increased risk for aortic aneurysm. When considered from this standpoint, a significant correlation is in fact observed. Example 1, for instance, demonstrates that the co-occurrence of AAA and macular degeneration markers was approximately 4-9 fold higher than that expected for a sample from the general population. This co-occurrence is significantly greater than would be expected by chance. Such results clearly are commensurate in scope with the current claims, which are directed to methods of assessing a subject's *risk* of aortic aneurysm at a location other than the eye. Furthermore, the Office Action ignores the results in Example 2 in which all individuals from a test group that had certain AMD markers also had a thoracic aortic aneurysm. So while not all individuals with macular degeneration may also have an aortic aneurysm, this application clearly demonstrates that such individuals are at significantly higher risk for an aortic aneurysm than the population generally. This in fact is what is currently claimed.

The fact that there is not necessarily a 1:1 correspondence between those that have macular degeneration and an aortic aneurysm at a location other than the eye does not mean that the claim is not enabled or lacks value. To the contrary, the currently claimed methods provide a useful means for readily identifying a high risk subpopulation from a larger population for whom further analysis is potentially warranted. Various conventional techniques can optionally be used with this high risk subpopulation to confirm whether an aneurysm is actually present (see, e.g., page 3, lines 30-31). The current methods then can in some respects be viewed as a useful screening tool.

Finally, Applicants address the concern that certain teachings in the application with respect to detecting elastin as an indicator of an aneurysm are at odds with teachings in the scientific literature. It is questioned, for example, how increases in elastin levels can serve as a marker for macular degeneration in view of statements in Grange (Cardiovascular Surgery 5:256-265 (1997)). Portions of Roberts (Atherosclerosis 140:281-295 (1998)) are cited for the proposition that detection of elastin in the blood is difficult (see Office Action , paragraph bridging pages 6 and 7). In response, Applicants submit that the teachings of these references have been mischaracterized due to failure to consider the complete teachings of these references. Furthermore, Applicants note that the current claims do not involve detection of elastin, thus rendering these concerns moot.

VI. Claim Rejections under 35 U.S.C. 112, second paragraph

Claims 1-7, 9, 10, 12, 19 and 36 are rejected under 35 U.S.C. 112, second paragraph as being indefinite. It is specifically stated that the claims to not include language indicating how to relate the finding steps with a diagnosis.

In response, Applicants note that claim 1 has been amended to indicate how one assesses whether a subject is at risk for an aortic aneurysm at a location other than the eye. Claim 1 now specifically states that a difference in the level of one or more protein markers relative to the level of the same marker(s) in a control population is an indication that the subject

is at risk for an aortic aneurysm at a location other than an artery in the eye. In view of this specific standard, it is submitted that this rejection should be withdrawn.

VII. Claim Rejections under 35 U.S.C. 103

Claims 1-7, 9, 10, 12, 19 and 36 are rejected under 35 U.S.C. 103(a) as allegedly being obvious over Nitatori in view of Schneider, Cunningham, Vingerling and further in view of Newsome and Satta. For the reasons that follow, Applicants respectfully disagree.

A. Cited Art

Nitatori simply discusses how certain MRI methods can be utilized to detect aortic aneurysms.

Schneider discusses the use of ICG videoangiography to distinguish between retinal macroaneurysms and damage caused by AMD. Schneider does not discuss at all, however, correlations between AMD and aneurysms located outside the eye.

Cunningham notes that in some instances aneurysms in the ophthalmic artery can co-exist with drussen in the retina. But there is no discussion or suggestion whatsoever regarding a possible correlation between macular degeneration and aneurysm at a location other than the eye.

Vingerling discusses a possible relationship between AMD and atherosclerosis. Vingerling goes on to note, however, that there have been a number of studies concluding that no such relationship exists (Vingerling, p. 407, first full paragraph). Moreover, there is no discussion regarding a correlation between macular degeneration and aneurysm, particularly aneurysms at a location other than the eye.

Newsome simply discusses studies in which certain antibodies were utilized to determine some of the components of drusen.

Satta only discusses the use of anti-elastin antibodies to detect the destruction of elastin in samples taken from abdominal aortic aneurysms.

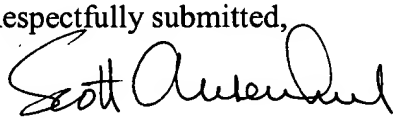
B. Cited Art Distinguished

These references fail to render the current claims obvious because, even when combined, all these references still fail to teach or suggest each and every element of the currently claimed invention as required to establish a prima facie case of obviousness.

For instance, the collective teachings of these cited references fail to teach or suggest a method in which one determines whether a blood, serum, plasma or urine sample from a subject has one or more protein markers for macular degeneration. Furthermore, the collected teachings of these references contain nothing to suggest that a difference in the level of the one or more protein markers relative to the level of the same marker(s) in a control population should be taken as an indication that the subject is at risk for an aortic aneurysm at some location other than the eye. Said differently, the cited art is completely lacking in any teaching or suggestion regarding the concept that one can correlate certain protein markers for macular degeneration with risk of aortic aneurysm at a location away from the eye. So for each of these reasons, it is submitted that this rejection be withdrawn.

If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 303-571-4000.

Respectfully submitted,



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